Paper No. 30

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KEITH V. WOOD and MONIKA G. GRUBER

Appeal No. 1999-1730
Application 08/478,205

ON BRIEF

Before ROBINSON, ADAMS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-17, 20-23, 25-27, 29, and 33. Claims 18 and 30-32 are also pending and have been indicated to be allowable. Paper No. 17, mailed December 19, 1997, page 1, and Examiner's Answer, page 2.

Claims 1 and 33 are representative of the claims on appeal and read as follows:

1. An isolated DNA molecule comprising a segment having a sequence which encodes a synthetic mutant beetle luciferase comprising an amino acid sequence that difeers from that of the corresponding wild-type luciferase by at least one amino acid substitution, the position of the amino acid substitution corresponding to a position in the amino acid sequence of LucPplGR of SEQ ID NO: 2 selected from the group consisting of position 215, 224, 232, 236, 237, 242, 244, 245, 248, 282, 283 and 348, wherein the mutant luciferase produces bioluminescence having a shift in wavelength of peak intensity of at least 1 nanometer relative to the bioluminescence produced by the wild-type luciferase.

33. An isolated DNA molecule comprising a segment having a sequence which encodes a mutant beetle luciferase having an amino acid sequence that differs from that of the corresponding wild-type luciferase LucPplGR by at least one amino acid substitution, wherein the encoded mutant luciferase is selected from the group consisting of LucPplGR-R_{223}L, -R_{223}Q, -R_{223}M, -R_{223}H, -L_{238}R, -L_{238}M, L_{238}Q, -L_{238}S, -L_{238}D, -S_{247}H, -S_{247}T, -S_{257}Y, -S_{247}F and the encoded mutant luciferase produces bioluminescence having a shift in wavelength of peak intensity of a least 1 nanometer relative to the bioluminescence produced by the wild-type luciferase.

The examiner relies on the following references:

Wood (Wood (1990)), "Luc Genes: Introduction of Colour into Bioluminescence Assays," Journal of Bioluminescence and Chemiluminescence, Vol. 5, pp. 107-114 (1990)

Wood (Wood dissertation) "Luciferases of Luminous Beetles: Evolution, Color Variation, and Applications," Ph.D. dissertation, University of California at San Diego, 1989.

Claims 1-17, 20-23, 25-27, 29, and 33 stand rejected under 35 U.S.C. § 103 as obvious over the Wood dissertation and Wood (1990).

We reverse.

Background

The specification reports that several luciferase-encoding cDNAs have been isolated from the beetle Pyrophorus plagiophthalamus. See page 8 (citing the Wood dissertation). These naturally occurring luciferases vary slightly in their amino acid sequences and produce light of different colors ranging from green to orange. Specification, page 7. The specification discloses numerous mutants of P. plagiophthalamus luciferase. See pages 14-16. The disclosed mutants contain amino acid variations which differ from those that occur naturally, and which affect the color of light produced by the mutant luciferases. See id.

Discussion

Claims 1-17, 20-23, 25-27, and 29 are directed to DNA encoding a mutant luciferases which have an amino acid substitution in a position that does not vary in the naturally occurring variants. Claim 33 is directed to DNA encoding a mutant luciferase which has a different amino acid substitution compared to the naturally occurring variants, albeit in one of the amino acid positions known to vary among the naturally occurring variants.

The examiner rejected all of the claims as obvious over the Wood dissertation and Wood (1990). The examiner reasoned that the Wood dissertation discloses cloning of naturally occurring P. plagiophthalamus luciferase variants and suggests that such variants, producing light of different colors, would be useful as reporter genes. Examiner's Answer, pages 5-6. The examiner noted that the Wood dissertation shows that changes in the amino acid positions recited in claim 33 (i.e., positions 223, 238, and 247) account for most

of the difference in color between the naturally occurring luciferase variants. Therefore, the examiner reasoned that

> one of ordinary skill in the art would reasonably expect that these positions must be important for defining the environment surrounding the luciferin substrate and therefore the color of the emitted light. One of ordinary skill in the art would reasonably expect that the introduction of other amino acids into these positions would produce mutant enzymes with additional colors of emitted light as each amino acid has different chemical properties (i.e., charge, polarity, hydrophobicity etc.) and therefore would alter the environment around the luciferin substrate in different ways.

Id., page 8.

The examiner also concluded that it would have been "obvious to mutate other amino acids within the region of amino acids 223-247." Id. She found motivation to do so based on the following passage in the Wood dissertation:

> The three substitutions that cause most of the color shift between yellow green and orange are located in a 25-amino acid segment of the sequences, from positions 223-247. The probability of this occurring by chance is about 0.01. . . . [I]t is likely that this region contains many, if not most, of the potentially suitable amino acids that affect the color of luminescence. It is expected that such a region would be close to the binding site of luciferin.

Wood dissertation, page 221.

Appellants argue that the cited references would not have rendered the claimed DNAs obvious to those of ordinary skill in the art. Appellants argue that the cited references would not have made it obvious to alter amino acid positions other than the three positions taught by the references to be important to light color, nor would they have made it obvious to make substitutions other than the naturally occurring variations at those three positions.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "'Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.' . . . [T]he same inquiry must be carried out in the context of a purported obvious 'modification' of the prior art." In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted, emphasis in original).

Evidence of motivation to combine may be derived from a variety of sources. "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citations omitted). As relevant here, "[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound." In re Lalu, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984).

A classic "obvious to try" situation is one in which the prior art would have made it obvious to "try each of numerous possible choices until one possibly arrived at a successful result, [but] the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Such is the case here. The cited references disclose that specific substitutions of specific amino acid residues of P. plagiophthalamus luciferase change the color of the light produced by the enzyme. The references do not suggest, however, that other substitutions at those positions would also affect the color of the emitted light. In particular, the references do not suggest any of the thirteen specific substitutions recited in claim 33. The references may have made it obvious to try making different substitutions at these positions, to see what effect various changes would have; they may even have provided a basis to expect that some of those substitutions would affect the color of the emitted light. But the references do not suggest the specific substitutions required to make the claimed products. Therefore, they support at best an "obvious to try" rationale, and "'obvious to try' is not the standard under § 103." In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1680.

The same is true for the rest of the rejected claims. The cited references may have made it obvious to try varying other amino acids in the luciferase enzyme, to find out which if any affected the color of the emitted light, but nothing in the references suggests altering the specific amino acid positions recited in claim 1. We disagree with the examiner's reading of the critical paragraph in the Wood dissertation. In relevant part, that passage states:

> The three substitutions that cause most of the color shift between yellow-green and orange are located in a 25-amino acid segment of the sequences, from positions 223-247. The probability of this occurring by chance is about 0.01. . . . [I]t is likely that this region contains many, if not most, of the potentially suitable amino acids that affect the color of luminescence. It is expected that such a region would be close to the binding site of luciferin.

Wood dissertation, page 221.

The examiner argues that "the passage points to a region of only 25 amino acids in length and suggests that this region will contain most of the amino acids which affect the color of luminescence. . . . Thus the reference clearly points to a specific region for the skilled artisan to go to produce further modifications of the prior art luciferase genes." Examiner's Answer, pages 10-11.

Appellants argue that the examiner has misinterpreted the relevant paragraph. Appellants interpret the paragraph as meaning "that the three known amino acid positions represent most of the potential sites where an amino acid change would result in a different color, and that few other suitable sites would be found." Appeal Brief, page 11.

We believe Appellants' interpretation is closer to how the passage would have been read by those skilled in the art, at the time the invention was made. The passage seems simply to summarize the experimental results disclosed and discussed in the Wood dissertation, by noting that the three most important positions for luciferase color (positions 223, 238, and 247) are located within 25 amino acids of each other. The passage notes that this is not likely to have occurred by chance and that most of the amino acids that affect color are likely to be in this area. That is, the reference to "many, if not most, of the potentially suitable amino acids that affect the color of luminescence" would have been understood to refer simply to the three positions that were disclosed in the

dissertation to be important. Only with the benefit of hindsight can this passage be read to suggest mutating other amino acids in the 223-247 region.

We therefore agree with Appellants that the cited references would not have motivated a person of ordinary skill in the art to alter the amino acid sequence of P. plagiophthalamus luciferase at the positions recited in claim 1. Since the references do not provide the requisite motivation to make the claimed product, they do not support a prima facie case of obviousness.

Summary

We reverse the rejection for obviousness because the cited reference do not provide the requisite motivation to modify the known compound as required to meet the limitations of the claims.

REVERSED

Douglas W. Robinson Administrative Patent Judge	)
Donald E. Adams Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Eric Grimes Administrative Patent Judge	)

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